Docket No.: 20523 US (C038435/0120240)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)

Chyi-Cheng CHEN and Bruno LEUENBERGER)

Serial No.: 09/726,880)

Filed: November 30, 2000)

For: **A VITAMIN POWDER COMPOSITION AND METHOD OF MAKING**)

Examiner: L. Channavajjala

Art Unit: 1611

DECLARATION OF BRUNO LEUENBERGER, Ph.D., UNDER 37 C.F.R § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Bruno Leuenberger, a Swiss citizen, declare as follows:

1. I received a Ph.D in Physical Chemistry from the University of Bern, Switzerland, in 1985. My postdoctoral work was done at the University of Virginia, Charlottesville, VA, USA, in 1986.

2. I have been employed by DSM Nutritional Products Ltd., Kaiseraugst, Switzerland ("DSM") or its predecessor, Roche Vitamins Division, Basel, Switzerland ("Roche Vitamins"), since 1987. DSM became my employer during or around December 2003.

3. Specifically, from 1987 to 1989, while working at Roche Vitamins, I was a Laboratory Leader, Product Formulation. During 1990, I was the Group Head of

Product Form Development Research. From 1991 to 2001, I was the Section Head of Carotenoid Formulation and the Project Manager of certain carotenoid-related projects. From 2001 to 2004, I was the Section Head of Product Form Development, Human Nutrition & Health and I was the Project Manager of several formulation projects. From 2004 to 2007, I was the Competence Manager, Product Form Concept & Design. From 2007 to the present, I have been a Corporate Scientist, Nutrition Formulation and Application. My work overall has involved development of product forms of carotenoids, vitamins and other health-related ingredients for feed, food, and pharmaceuticals, with emphasis on formulation of sparingly soluble actives and controlled release. I have also investigated raw materials, especially protective colloids, for the development of new product forms. In addition, I have evaluated new formulation technologies, especially pertaining to micronization, emulsification and solidification. A copy of my Curriculum Vitae is enclosed as Exhibit A.

4. The present application discloses and claims a powder composition comprising at least one fat-soluble vitamin dispersed in a matrix consisting of an emulsion-forming composition selected from the group consisting of a natural polysaccharide gum, a mixture of polysaccharide gums, a protein, a mixture of proteins, and mixtures thereof, wherein the fat-soluble vitamin is present in the powder composition in the form of solid droplets having an average diameter of about 80 to about 120 nanometers (nm) and wherein the fat-soluble vitamin is present in the powder composition in the amount of from about 10% to about 30% by weight. The fat-soluble vitamin may be, for example, vitamin E or its esters, vitamin A or its esters, vitamin K (phytomenadione), vitamin D_3 (cholecalciferol), and mixtures thereof. The specification

discloses that the fat-soluble vitamin "may be used in pure form, or in a suitable diluent such as a fat or edible oil (e.g. soybean oil). Thus the droplets in the powder of this invention may contain one or more vitamins in an appropriate diluent." (Page 10, lines 5-7.)

5. The specification also discloses that "[t]he invention contemplates powder compositions which, when added to a liquid, provide vitamin droplets averaging about 70 to 200 nm in diameter, ... preferably about 80 to about 120 nm.... When the liquid is optically clear, then the liquid remains for all practical purposes optically clear after addition of a powder composition according to this invention." (Page 6, lines 19-24.) The specification also discloses that "[t]he compositions of this invention may ... be added to liquids that are not optically clear, [yet] increase in turbidity is not of concern. Ringing will not occur." (Page 6, lines 17-19.)

6. The specification further discloses that "[o]ptical clarity (turbidity) can be measured by a turbidimeter." (Page 5, lines 27-28.) Furthermore, "[t]urbidity is measured by directing a beam of light into a cell containing a test sample, measuring the amount of light that is reflected at a 90 degree angle by any droplets present in the sample and comparing it to the light scattered by a standard reference suspension. ... The amount of reflected light is directly proportional to the degree of turbidity. NTU (Nephelometric Turbidity Unit) is customarily used to describe the results from the turbidity measurement using a turbidimeter. Higher NTU means higher turbidity." (Page 6, lines 3-11.) The specification further discloses that "optical clarity (NTU) is a function of the droplet size of the composition." (Page 23, lines 4-5.) This is indicated, for example, in Figure 2, which "shows a graph of droplet size (nm) versus optical clarity

(NTU) for 15.75%(wt) vitamin E (circle) and 26.25%(wt) vitamin E (square) in water dispersion." (Page 4, lines 9-10; Fig. 2.) As can be seen in the graph, the optical clarity (NTU) of a claimed powder composition which is in a water dispersion is lower, i.e., improved, for emulsion droplet particles between about 80 to about 120 nanometers (nm), than for emulsion droplet particles above that particle size range. (Fig. 2.)

7. As noted above, the application discloses and claims that the matrix in which the fat-soluble vitamin is dispersed consists of an emulsion-forming composition selected from the group consisting of a natural polysaccharide gum, a mixture of polysaccharide gums, a protein, a mixture of proteins, and mixtures thereof. The specification discloses that "[t]he polysaccharide gum and/or the protein, as used in this invention both have sufficient emulsifying properties. This means that they have sufficient emulsifying properties in an oil-in-water context to emulsify the oil into a fine dispersion in an aqueous medium and are capable of forming a stable emulsion of a desired droplet size ... under conditions of high pressure homogenization." (Page 6, lines 26-31.) Whether a selected polysaccharide gum or a protein has an emulsifying capacity sufficient for use in the claimed invention may be easily determined by assaying whether or not the selected polysaccharide gum and/or protein can maintain an emulsion as defined above, and as further described..." (Page 7, lines 7-11.) The protocol that one skilled in the art can use to determine whether or not a potential matrix component has a sufficient emulsifying capacity and is thus suitable for use in accordance with the claimed invention can be found in the specification at page 7, lines 12-23. Further information regarding the matrix component can be found in the

specification from page 6, line 31 to page 7, line 6, and page 7, line 26 to page 9, line 28.

8. In addition, the present application discloses and claims a powder composition comprising at least one fat-soluble vitamin dispersed in a matrix of an emulsion-forming composition selected from the group consisting of a natural polysaccharide gum, a mixture of polysaccharide gums, a protein, a mixture of proteins, and mixtures thereof, wherein the fat-soluble vitamin is present in the powder composition in the form of solid droplets, wherein the powder composition is produced by a process comprising: (a) combining water with a matrix component selected from the group consisting of a natural polysaccharide gum, a mixture of polysaccharide gums, a protein, a mixture of proteins, and mixtures thereof, to form a solution; (b) adding a fat-soluble vitamin to the solution to form a crude emulsion, wherein the fat-soluble vitamin is added in an amount to provide from about 10% to about 30% by weight fat-soluble vitamin in the powder composition; (c) emulsifying the crude emulsion at a temperature of from about 5° C to about 75° C at a pressure of from about 10,000 psi (about 680 bar) to about 60,000 psi (about 4080 bar), to obtain an emulsion in which the droplets have an average diameter of about 70 to about 200 nm; and (d) drying the emulsion to obtain the powder composition. The specification discloses that "[i]n order to attain the desired droplet size, the emulsion step ... may be repeated through one or more passes as necessary to obtain the desired droplet size, i.e., the crude emulsion is passed into the homogenization vessel, emulsified, passed out of the homogenization vessel, and passed through the homogenization vessel again until the desired droplet size is attained." (Page 21, lines 12-16.) The specification provides guidance in

disclosing that "[u]sually at least five to twenty passes will be required." (Page 21, line 16.) It is further disclosed that "[e]mulsification passes should continue until testing shows that the desired droplet size is achieved as determined by particle size analysis (for example, by light scattering...). It is important that the homogenization step be performed at an ultra-high pressure as described ... to effectively reduce the droplet size of the emulsion to a desirable size." (Page 21, lines 23-29.) As disclosed, "homogenization" refers to "further emulsification." (Page 26, lines 4-5.) The specification also discloses that "the droplet size of the emulsion determines the droplet size in the resulting powder..." (Page 22, lines 8-11, and page 23, lines 25-30.) Emulsification may be continued, for example, until the droplets in the emulsion have a preferred average diameter of from about 80 to about 120 nm. (Page 21, line 27 to Page 22, line 7.)

9. I am aware that an Office Action issued on April 1, 2009, with regard to the present application. (Paper No. 20090330.) It is my understanding that in the Office Action, the Examiner asserted that claims 1, 3-14, and 17 are not patentably distinct from U.S. Patent No. 5,968,251 to Auweter et al. ("Auweter") alone, or in view of EP 937412 to Stein et al. ("Stein"). (Id. at 2.) The Examiner has relied on these documents as disclosing and/or suggesting a powder composition comprising at least one fat-soluble vitamin dispersed in a matrix consisting of an emulsion-forming composition selected from the group consisting of a natural polysaccharide gum, a mixture of polysaccharide gums, a protein, a mixture of proteins, and mixtures thereof, wherein the fat-soluble vitamin is present in the powder composition in the form of solid droplets having an average diameter of about 80 to about 120 nanometers (nm) and

wherein the fat-soluble vitamin is present in the powder composition in the amount of from about 10% to about 30% by weight. (Id. at 2-3.)

10. It is also my understanding that in the Office Action, the Examiner asserted that claim 15 is not patentably distinct from Auweter alone or in view of Stein and U.S. Patent No. 3,886,294 to Emodi et al. ("Emodi"). The Examiner has relied on these documents as disclosing and/or suggesting a powder composition as indicated in paragraph 9 above, wherein the composition further comprises from about 60 to 85% by weight of a matrix component, based on the total weight of all the components present in the composition, and the composition has a moisture content of about 1-4% by weight.

11. I am familiar with Auweter cited in the pending Office Action. Auweter discloses that carotenoids are "entirely insoluble" in water. (Col. 1, lines 42-51.) Auweter set out to prepare coloring compositions using carotenoids, and sought to overcome the "poor coloring results" that had previously been obtained due to the insolubility of carotenoids. (Id.)

12. Auweter further discloses "coldwater-dispersible dry powders which contain carotenoids and are obtainable [by the process disclosed] and which have different color effects depending on the production variant." (Col. 1, lines 26-29.) Auweter also discloses that the "[c]arotenoid preparations in the form of coldwater-dispersible powders are produced by

> a) preparing a molecular-disperse solution of a carotenoid, with or without an emulsifier and/or an edible oil, in a volatile, water-miscible, organic solvent at elevated temperature and adding therein an aqueous solution of a protective colloid, whereupon the hydrophilic solvent component is transferred into the aqueous phase, and

the hydrophobic phase of the carotenoid results as [the] nanodisperse phase,

b) heating the resulting hydrosol at from 40° C. to 90° C., with or without cooling of the hydrosol to from 0° C. to 30° C. beforehand, and

c) removing the solvent and the water from the heated hydrosol, and converting it into a water-dispersible dry powder. (Abstract.)

Auweter discloses that the molecular disperse solution according to process step a) can be carried out "under atmospheric or superatmospheric pressure." (Col. 2, lines 47-54.) According to Auweter, "[s]uperatmospheric pressure, *e.g.* in the range from 20 bar to 80 bar, preferably 30 to 60 bar, may be advantageous for rapid preparation of the molecular-disperse solution." (Col. 2, lines 59-62.) Auweter also discloses that in example 1, "[t]he ... process took place under 30 bar..." (Col. 6, line 48-49.)

13. "Examples of protective colloids which are used" in accordance with Auweter are said to be "gelatin, fish gelatin, starch, dextrin, vegetable proteins, pectin, gum arabic, casein, caseinate or mixtures thereof." (Col. 4, lines 40-42.) Auweter discloses that "it is also possible to employ polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose and alginates." (Col. 4, lines 43-46.)

14. Auweter also discloses that "[t]he result is a dry powder which, on use of a water-soluble colloid, can be dissolved again in water to obtain a uniform dispersion of the active substance with particle sizes in the range below 1 µm. The active substance hydrosol obtained in this way proves to be extremely stable..., despite the fine particles." (Col. 5, lines 28-34.) Auweter further discloses that "[t]he preparations according to the invention are, by reason of their good coldwater dispersibility, outstandingly suitable as coloring agents ..." (Col. 5, lines 35-37.) In

addition, Auweter discloses that one of the process variants results in "the precipitated active substance particles after heating [being] essentially spherical with a diameter of, typically, 200 nm." (Col. 3, lines 52-57.) There is no disclosure in Auweter of any particle size of precipitated active substance that does not have at least a 200 nm diameter in one direction.

15. Auweter further discloses that Example 1, which includes β-carotene, dl-α-tocopherol, and gelatin, "[resulted] in a colloid-disperse β-carotene dispersion with a yellow hue. Spray drying the dispersion resulted in a free-flowing dry powder which forms a clear yellow dispersion in water." (Col. 6, lines 47-48 and 52-58.) In Example 2, it is disclosed that "β-[c]arotene was precipitated in colloid-disperse form as described in Example 1." (Col. 6, lines 61-62.) Auweter further discloses that upon processing, Example 2 "[resulted] in a colloid-disperse β-carotene dispersion with an orange hue. Spray drying of the dispersion resulted in a free-flowing dry powder which forms a clear orange dispersion in water." (Col. 6, line 61 to Col. 7, line 2.)

16. I am also familiar with Stein cited in the pending Office Action. Stein discloses "a continuous process for the preparation of a pulverous carotenoid, retinoid or natural colourant preparation, wherein the active ingredient is finely divided ...." (Abstract). The process includes the steps of:

> a) forming a suspension of the active ingredient in a water-immiscible organic solvent optionally containing an antioxidant and/or an oil,
> b) feeding the suspension of step a) to a heat exchanger and heating said suspension to 100-250°C, whereby the residence time in the heat exchanger is less than 5 sec,
> c) rapidly mixing the solution of step b) at a temperature in the range of 20-100°C with an aqueous solution of a swellable colloid optionally containing a stabilizer,
> d) removing the organic solvent and

e) converting the dispersion of step d) into a pulverous preparation. (Col. 2, lines 3-16.)

The "finely divided" starting material is said to be of "a particle size of less than 1.5 micron, preferably less than 1 micron, more preferably less than 0.4 micron." (Col. 2, lines 18-21.) Stein further discloses that the "swellable colloid" can include gelatin, carbohydrates, dextrin, pectin, gum arabic, octenylbutanedioate amylodextrin, milk proteins, and vegetable protein, or mixtures thereof. (Col. 3, lines 2-8.) Stein also discloses that powders formed from the compositions are soluble in cold water and provide coloration. (See Examples 1-5.)

17. I am also familiar with the Declaration of Mr. Hermann Stein Under 37 C.F.R. § 1.132 dated March 16, 2005 ("the Stein Declaration"), which is of record. I understand that the Stein Declaration was provided to the U.S. Patent and Trademark Office with the Submission Under 37 C.F.R. § 1.114; Response to Final Office Action on March 24, 2005 (which was received in the U.S. Patent and Trademark Office on March 28, 2005). It is noted that the Declarant of the Stein Declaration, Mr. Hermann Stein, is the same Hermann Stein who is an inventor of the Stein document cited by the Examiner. A copy of the Stein Declaration is attached as Exhibit C.

18. I am also familiar with Emodi cited in the pending Office Action. Emodi discloses "[l]iquid and powder carotenoid coloring compositions suitable for the preparation of optically clear, stable aqueous solutions, and the preparation thereof..." (Abstract, lines 1-3.) Emodi also discloses that "[t]he composition [consists] of one or more carotenoid coloring substances, an antioxidant and an emulsifier ingredient comprising a polysorbate and a mixture of monoglycerides of low molecular weight saturated coconut fatty acids and up to two optional emulsifier components selected

from the group consisting of a mixture of saturated fractions of coconut oil triglycerides and a polyoxyethylene (40) stearate wax." (Abstract, lines 3-11.) Emodi further discloses that "[t]he carotenoid coloring compositions, ... whether in the liquid or powder form, contain from about 0.1 to about 2.0 percent by weight, preferably from about 0.3 to about 1.0 percent by weight of the carotenoid coloring agent." (Col. 2, lines 13-17). Each of the powder composition examples, Examples 1, 2, and 4-7, includes either 0.3 percent, 0.5 percent, or 1 percent of a carotenoid compound. (Col. 4, line 50 to Col. 5, line 39, and Col. 6, line 1 to Col. 7, line 41.) The powder form of Emodi's compositions is also said to include "a water-soluble carrier composition which comprises a sugar, e.g., sucrose, fructose, lactose, invert sugar and the like and a water-soluble colloid-former such as, for example, hydrolyzed gelatin, low or high bloom gelatin and mixtures of hydrolyzed cereal solids and sugar..." (Col. 2, lines 25-33.) In addition, Emodi discloses that "aqueous solutions of the compositions ... formed from the various liquids and powders can be passed through a filter which will retain particles larger than 0.22 micron without loss of color." (Col. 4, lines 30-34.)

19. Emodi also discloses that "the powdered carotenoid coloring compositions of the invention are prepared by initially forming a supersaturated carotenoid liquid [which is] prepared by heating the combined components of the emulsifier ingredient and the preservative and dissolving the carotenoid coloring agent therein. A temperature of from about 80° to about 140°C. preferably from about 100° to about 120°C. is contemplated." (Col. 4, lines 6-9 and Col. 3, line 63 to Col. 4, line 1.) Emodi further discloses that the supersaturated carotenoid liquid "while still at the formation temperature, i.e. preferably at a temperature of from about 100° to 120°C., [is

added] to a previously formed aqueous solution containing the carrier composition, i.e. the soluble colloid-forming component, sugar and preservatives. The combined solutions are thereafter spray dried utilizing conventional spray drying equipment. The resultant spray dried powder is composed of submicroscopic droplets of a solution of a carotenoid coloring material in emulsifier ingredient encased in a water soluble colloidal film." (Col. 4, lines 9-19.) Example 1 of Emodi is said to provide a powder preparation containing 0.5 percent by weight β-apo-8'-carotenal. The spray dried powder is disclosed as "having a moisture content of less than 2 percent by weight." (Col. 4, line 50 to Col. 5, line 12.)

20. As noted above, the claimed powder composition achieves optical clarity. (See, e.g., ¶¶ 5-6 above.) The specification describes that there is a direct relationship between the amount of light reflected from any droplets present and the degree of turbidity which is reported in units of NTU (Nephelometric Turbidity Unit). (See ¶ 6 above.) As also noted above, the specification discloses that optical clarity (NTU) is a function of the droplet size of the claimed composition, as shown in Figure 2. (See ¶ 6 above.)

21. The general relationship between turbidity of lipid vesicle suspensions and particle size is indicated, for example, in Pozharski *et al.*, Relationship Between Turbidity of Lipid Vesicle Suspensions and Particle Size, (2001) 291, 158-162 (received September 15, 2000) ("Pozharski"). (Exhibit B.) As can be seen in Figure 1 on page 159, turbidity is very low for particles having smaller diameters. For particle diameters below 200 nm, turbidity approaches zero. Pozharski discloses that the "size-

turbidity dependence [data, including data not shown, indicates] that such behavior is inherent in the properties of lipid vesicles as light scatters." (Page 159, lines 2-7.)

22. Furthermore, at a particle size of about 200 nm, particles are at a transitional point between the invisible and visible ranges of the spectrum. At decreasing particle sizes below 200 nm, particles enter a size range which is not visible to the eye. Particles having an average diameter in a range of from about 80 to about 120 nm are in the invisible size range. Based on the foregoing, I believe that these particles are small enough to allow sufficient transmission of light such that a clear liquid in which a powder composition having such particles is added appears as a transparent and/or translucent solution which is essentially free from turbidity. Thus, the claimed average diameter particle size range of about 80 to about 120 nm of the fat soluble vitamin in the form of solid droplets is integral to the favorable aspects achieved with the claimed powder composition of optical clarity and a transparent and/or translucent solution upon addition to a clear liquid.

23. The physicochemical properties of carotenes such as β-carotene and fat-soluble vitamins such as α-tocopherol, for example, are known to differ markedly. See, *e.g.*, selected portions of The Merck Index, Fourteenth Ed. 2006 ("The Merck Index"), attached as Exhibit D. As indicated in the entry for β-carotene in The Merck Index, β-carotene is "[p]ractically [insoluble] in water", and its melting point is 183°C. (Exhibit D, page 1854, lines 15 and 19.) Thus, β-carotene is an insoluble solid compound. The use indicated is as a "[y]ellow coloring agent for foods." (Exhibit D, page 1854, line 26.) The melting point of α-tocopherol, on the other hand, is 2.5-3.5° C. (Exhibit D, page 9494, under the structure of α-tocopherol.) Thus, α-tocopherol is a

liquid oil, and it is known to be light or amber yellow in color. The physicochemical properties of β-carotene and fat-soluble vitamins differ in significant ways that affect the relative goals in formulating. In looking to formulate a liquid oil to achieve a powder composition having optical clarity, i.e., being essentially free from turbidity in solution, and resulting in a transparent and/or translucent solution in a clear liquid, one skilled in the art would not have looked to technologies for formulating a solid, insoluble, colored compound which are for preparing compositions having color effects.

24. In view of my extensive knowledge in the field, it is my understanding that given the stated goal of each of Auweter, Stein, and Emodi of providing powder coloring compositions, colorant particles in the disclosed formulations of these documents would have an average diameter range such that the particles would be visible to the eye.

25. From my review of Auweter, it is my understanding that Auweter provides a β-carotene powder composition that renders β-carotene, which is otherwise insoluble, dispersible as fine particles in cold water. It is also my understanding that the dispersion disclosed by Auweter is a solid in liquid dispersion stabilized with colloids. In view of the foregoing and Auweter's disclosed particle size of about 200 nm, it is my understanding that the coldwater-dispersible powder composition, when added to a previously clear liquid, would produce a turbid and colored solution. This is consistent with Auweter's stated goal of a coldwater-dispersible powder composition that provides color effects.

26. It is my opinion that the coldwater-dispersible composition of Auweter is significantly different from the presently claimed powder composition.

Auweter's β-carotene powder composition provides fine particles of β-carotene which would disperse as solid particles in liquid, whereas the claimed powder composition provides solid droplets of a fat-soluble vitamin dispersed in a matrix consisting of an emulsion-forming composition selected from the group consisting of a natural polysaccharide gum, a mixture of polysaccharide gums, a protein, a mixture of proteins, and mixtures thereof. The claimed emulsion-forming composition has sufficient emulsifying properties in an oil-in-water context to emulsify the oil into a fine dispersion in an aqueous medium and forms a stable emulsion of the claimed droplet size. Whereas Auweter's β-carotene powder composition having particle sizes of about 200 nm would produce a turbid and colored solution, the claimed powder composition having solid droplets of fat soluble vitamin with an average diameter of about 80 to about 120 nm achieves optical clarity and a transparent and/or translucent solution upon addition to a clear liquid.

27. Based on the foregoing, Auweter provides no motivation for one skilled in the art to achieve the claimed powder composition. In fact, the use of β-carotene in Auweter to provide color effects is antithetical to the claimed powder composition which achieves optical clarity and a transparent and/or translucent solution upon addition to a clear liquid. Auweter's disclosure of "precipitated active substance particles ... with a diameter of, typically, 200 nm", a particle size which would appear visible in an otherwise clear solution, also flies in the face of obtaining the claimed powder composition which comprises solid droplets of a fat-soluble vitamin having an average diameter of about 80 to about 120 nm, which droplets are <u>not</u> in the visible range.

28. Auweter does not disclose a process using an emulsion-forming composition that has sufficient emulsifying properties in an oil in water context to form a stable emulsion of the claimed droplet size. Auweter's process differs from the process used in making the claimed powder composition. Auweter discloses how to make a solid in liquid dispersion of fine particles of β-carotene stabilized with colloids. Furthermore, Auweter provides no guidance as to how the presently claimed composition could be produced. For example, Auweter's disclosure of the use of atmospheric or superatmospheric pressure, e.g., in the range of 20 to 80 bar, preferably 30 to 60 bar, to produce a cold-water dispersible powder, provides no indication to use a high-pressure homogenization process, as disclosed.

29. Even if one were to consider using greater pressure, although Auweter provides no suggestion of this, the literature indicates that pressure is not a result-effective variable in relation to the diameter of particles in an emulsion. For example, Desrumaux and Marcand investigated the effect of pressure on the emulsification of sunflower oil (20%) in water using an ultra-high-pressure homogenizer. Desrumaux, A. and Marcand, J., Formation of Sunflower Oil Emulsions Stabilized by Whey Proteins with High-Pressure Homogenization (up to 350 MPa); Effect of Pressure on Emulsion Characteristics, *Intl J. Food Science and Tech.* (2002) 37, 263-269 ("Desrumaux"). (See Exhibit E.) Desrumaux discloses:

> Homogenization reduced the Sauter diameter appreciably, the reduction increasing with treatment pressure from 50 to 90 MPa (Fig. 4). This result agrees with the study of Robin *et al.* (1992), who observed a decrease in the droplet average size between 7.8 and 76.3 MPa. Above 90 MPa, the [droplet diameter] increased with pressure (Fig. 4) and then stabilized approaching 200 MPa. Robin *et al.* observed a similar plateau of the droplet size diameter, but between

> 60 and 76.3 MPa.... Above 200 MPa, the [droplet diameter] decreased and then increased again at around 250 MPa. However, there was a final decrease of [droplet diameter] above about 300 MPa." (Page 267.)

Robin *et al.*, Microfluidization of Dairy Model Emulsions. I. Preparation of Emulsions and Influence of Processing on the Size Distribution of Milk Fat Globules (1992) *Lait*, 72 511-550 ("Robin"), which is cited by Desrumaux, is also attached as Exhibit F. Thus, the literature indicates that particle diameter has no consistent relation to pressure.

30. It is my understanding that the process of Stein is similar to the process of Auweter in achieving their mutual goal of preparing carotenoid powder compositions for use as colorants. The principle difference between the processes is that Auweter discloses the use of a water-miscible organic solvent, whereas Stein discloses the use of a water immiscible organic solvent in the first step of forming a suspension of a carotenoid. I am not aware of any reason why the very similar processes of Stein and Auweter would not achieve substantially the same results in terms of carotenoid particle size. Moreover, I would expect that the processes of Stein and Auweter would produce carotenoid particle sizes in a comparable range.

31. In the Stein Declaration, Mr. Hermann Stein declares that "[d]uring the research that led to the invention disclosed in Stein, my co-inventors and I, using the knowledge available at the time, attempted to produce the smallest possible particle size." (Paragraphs 6, lines 1-3.) Stein reproduced Example 5 of Stein, "with a view toward optimizing the process by producing the smallest particle size." (Paragraph 6, lines 3-4.) Example 5, which is found at Col. 6, paragraphs 54-58 of Stein, is also reprinted in paragraph 6 of the Stein Declaration.

32. Stein declares that "[a]s Example 5 shows, at that time, at best we could produce particle sizes of about 196 nm. (Paragraph 7, lines 1-2.) Stein also declares that "[b]ased on my unique knowledge of the methods and compositions of Stein, and my long experience in the area of the production carbohydrate matrices, it is my opinion that one of skill in the art at the time of the above-captioned invention familiar with the disclosure of Stein could not have produced particles of the presently claimed size." (Paragraph 7, lines 2-6.) Stein further declares that "it is also my opinion that one could not have predicted that the process of the present invention would produce significantly smaller particle sizes than the methods of Stein." (Paragraph 8.)

33. I agree with H. Stein's analysis and conclusions. Accordingly, in view of all of the foregoing, it is my opinion that one skilled in this art could not have predicted from Auweter alone or in view of Stein that the claimed powder composition could be produced having a fat soluble vitamin in the form of solid droplets having an average diameter of about 80 to about 120 nm, and which achieves optical clarity and a transparent and/or translucent solution upon addition to a clear liquid.

34. Emodi's disclosure of powder carotenoid coloring compositions having only about 0.1 to about 2.0 percent by weight, preferably from about 0.3 to about 1.0 percent by weight of a carotenoid coloring agent, in addition to the required emulsifiers, does not suggest the claimed powder composition having a fat-soluble vitamin in the amount from 10% to about 30% by weight of the composition. In view of Emodi, one skilled in the art would have been led toward low percentages of active substance in combination with emulsifiers, rather than to the claimed powder composition. Also, it is my understanding that Emodi's disclosure that various liquids

and powders can be passed through a filter which retains particles larger than 0.22 micron without loss of color indicates that Emodi's powder contains particles larger than 0.22 micron, and that colored particles retained in the filtered solution have a particle size in the visible range.

35. In view of the foregoing, it is further my opinion that one skilled in the art could not have predicted from Auweter alone or in view of Stein and Emodi that the claimed powder composition could be produced having a fat soluble vitamin in the form of solid droplets having an average diameter of about 80 to about 120 nm which is present in the powder composition in the amount of from about 10% to about 30% by weight, and having from about 60 to 85% by weight of a matrix component based on the total weight of all the components present in the composition, wherein the composition has a moisture content of about 1-4% by weight, and achieves optical clarity and a transparent and/or translucent solution upon addition to a clear liquid.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 12. Nov. 09

Bruno Leuenberger

Short Curriculum Vitae of *Dr. Bruno H. Leuenberger*

Work Field:	Development of product forms of carotenoids, vitamins and health ingredients for the industry segments feed, food and pharma; with special emphasize on formulation of sparingly soluble actives and controlled release. Search for novel raw materials, especially protective colloids, for the development of new product forms. Evaluation of new formulation techniques and technologies, especially in the field of micronization, emulsification and solidification. Collaboration with Marketing and Production for existing and new product forms. Collaboration and network building with external partners and universities in the field of formulation and application.
06/07 - today	Corporate Scientist Nutrition Formulation and Application
10/04 – 05/07	Competence Manager Product Form Concept & Design
06/01 - 09/04	Section Head of Product Form Development Human Nutrition & Health. Project Manager of several formulation projects.
01/91 - 05/01	Section Head of Carotenoid Formulation. Project Manager of selected carotenoid projects. Promotions: 2000 Scientific Expert 1998 Power of attorney (Prokura) 1994 Power to act (Handlungsvollmacht)
01/90 -12/90	Group Head of Product Form Development Research.
03/87 -12/89	Laboratory Leader Product Formulation, Roche Vitamins Division, Basel.
1986	Research Associate, Institute of Chemistry, University of Virginia, Charlottesville, VA, USA.
1985	Dr. phil. nat., Physical Chemistry, University of Bern, Switzerland
1982	Lic.phil.nat / diploma in chemistry, University of Bern, Switzerland